

TOPICALLY APPLIED NSAIDs IN THE TREATMENT OF PAIN

The mainstay of management of inflammation and pain associated with arthritis and soft tissue injuries has been oral nonsteroidal anti-inflammatory drugs (NSAIDs). Topically applied NSAID products are not readily available in N. America for two reasons: 1) extensive studies of efficacy and toxicity by the topical route are very limited, and 2) most NSAIDs have lost their patents which makes them unprofitable for drug companies. Nevertheless, topical NSAIDs are widely available and are prescribed extensively in other regions. Topical NSAIDs have four major advantages: 1) higher concentrations of NSAIDs are delivered to the desired site (e.g. up to 100 times higher NSAID occurs in synovial fluid compared to that from NSAID blood levels; 2) only 1-3% of NSAID is systemically absorbed, reducing the possibility of gastrointestinal upset or ulcers; 3) low blood levels reduce the incidence of drug interactions; 4) low skin irritation at the application site.

PHLOJEL[®] Ultra can be used effectively to treat pain and inflammation by combining it with NSAIDs that penetrate the skin at the site of pain.

The advantages are tremendous!

More drug where the pain exists with little or no side effects!

This means there's very little chance for stomach ulcers or other painful internal maladies.

Patients tell us

- there is no stomach upset because the gel is applied directly to the area that hurts.
- relieves pain quickly
- they've been able to reduce and, in some case, eliminate the need for narcotic pain killers
- they can use NSAIDS in PHLOJEL[®] Ultra in combination with all their other medications without drug interaction problems
- they're seeing fantastic results with this type of topical therapy

The following list of abstracts illustrate the possible advantages of topical application of NSAIDs.

Gevi, M and Merlo, M., "Ketoprofen lysine by topical route in sports traumatology", *Current Therapeutic Research*, 34, 844-850 (1983).

Systemic absorption of the active drug after cutaneous application of a 5% gel of ketoprofen lysine was determined in 5 healthy volunteers and was shown to be very low (about 1%). A clinical trial was carried out on 30 sporting patients with various traumatological affections. Spontaneous pain, pain at passive movement, and at pression, swelling were evaluated before and after treatment. The new dosage form was endowed with a high analgesic and anti-inflammatory activity after topical use. Therapy was most effective against spontaneous pain with patients in sports and the very good results obtained on swelling confirmed its high anti-edema activity. The gel was well-tolerated with neither topical or systemic side effects being reported. It was concluded that 5% ketoprofen gel was very useful both as a resolutive and as a supporting therapy of surgery, plaster, or electromedical applications.

Ballerini, R., Casini, A. et al., "Study on the absorption rates of ketoprofen topically-administered in man: Comparison between tissue and plasma levels", *Int. J. Pharm. Res.*, VI, 69-72 (1986).

The transcutaneous passage of ketoprofen after a topical gel administration and its distribution to the inner part of the knee joint was evaluated in 6 patients. The ketoprofen concentration detected was 4.7 mcg/g in the intra-articular adipose tissue, 2.35 mcg/g in the capsular sample and 1.4 mcg/g in the synovial fluid. Plasma samples were also examined. The fluid samples from patients using topical ketoprofen were about 100 times higher in tissues than in plasma drawn at the same time. Since synovial fluid concentrations were also 100 times higher than in plasma, it is assumed that this occurred due to transcutaneous absorption from topical ketoprofen.

Flouvat, B., Roux, A., Dehotal-Landes, B., "Pharmacokinetics of ketoprofen in man after repeated percutaneous administration", *Arzneimittel Forschung*, 39, 812-815 (1989).

A topical formulation of ketoprofen was tested on 10 healthy subjects receiving a daily dose of 2.5% ketoprofen gel corresponding to 375 mg of the oral dose. Plasma samples were collected after the first dose and after 10 days of chronic treatment. Urine was also collected. Plasma concentrations were only 2.6% of the daily dose applied. No sign of local intolerance was noted.

Rau, R. and Hockel, S., "Piroxicam gel versus diclofenac gel in activated gonarthrosis", *Fortschr. Med.*, 107, 485-488 (1989).

In a single-blind comparative study 97 patients suffering from activated gonarthrosis were treated with either 4 x 40 mg of diclofenac gel or 4 x 5 mg piroxicam gel. Owing to

protocol violations, 28 patients were not included in the statistical evaluation. During the course of the treatment, a marked decrease in signs and symptoms was observed in the 69 patients included in the evaluation. In 80% of the patients, the treating physician assessed the efficacy of piroxicam gel as "good" or "excellent", in only 20% it was assessed as "moderate". In the diclofenac group, assessment of the results was positive in 74% of the patients. In 24% of the patients of this group, the physician's assessment of the success of the treatment was "not satisfactory". The majority of physicians and patients were satisfied with the toleration of the drugs used in this study. Only 2 patients (5.6%) of the piroxicam group and 4 patients (12.2%) of the diclofenac group were critical of local tolerance. The results of this clinical trial show that the preparations used here are appropriate for local therapy of distortions of the ankle joint.

Baixauli, F., Ingles, F., et al., "Percutaneous treatment of acute soft tissue lesions with naproxen gel and ketoprofen gel", *J. Int. Med. Res.*, 18, 372-378 (1990).

A randomized independent group, single-blind study was performed to compare the analgesic efficacy and the local and cosmetic tolerability of 3-5 cm of 10% naproxen gel with 10% ketoprofen gel in 30 patients complaining of moderate or severe pain due to acute soft tissue lesions. Both drugs were administered topically and were applied to the painful area at once every 12 hours as required. Efficacy and tolerability of both naproxen gel and ketoprofen gel were comparable, although naproxen gel produced a significantly greater reduction in pain on deep palpitation by the third day.

White, S., "Topical Non-steroidal Anti-inflammatory Drugs (NSAIDs) in the Treatment of Inflammatory Musculoskeletal Disorders", *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 43, 209-22 (1991).

The study showed that benzydamine HCl 3% cream clinically improved reduction of painful and inflammatory symptoms of traumatic injuries of soft tissues and joints. Piroxicam gel, 0.5%, also yielded clinical improvement in patients with traumatic injuries and osteoarthritis of the knee and muscular pain. Felbinac gel, 3%, alleviated pain in patients with soft tissue injuries. Adjunct therapy using ultrasound was useful. Pharmacokinetic data showed that the agents penetrate the skin and reach the underlying tissues, including synovial fluid. Plasma levels after topical administration are low. It is concluded that topical NSAIDs are particularly useful for the short-term treatment of acute musculoskeletal pain and inflammation and have less, and less serious, side effects than oral NSAIDs.

Willmann, H., Walde, P., et al., "Lecithin organogel as matrix for transdermal transport of drugs", *J. Pharm. Sci.*, 81, 871-874 (1992).

Organogels obtained by adding small amounts of water to a solution of lecithin in organic solvents were studied as matrices for the transdermal transport of drugs. Gels obtained from isopropyl palmitate and cyclohexane were used (molar ratios of water to lecithin of 3 and 12, respectively). Preliminary histological studies showed that the gels had no harmful effects when applied to the skin for prolonged periods. Data relative to

the stability of the organogels with time were also presented. Scopolamine and broxaterol were used as model drugs and the transdermal experiments were done with a Franz diffusion cell system using human skin obtained from plastic surgery. The transport rate of scopolamine obtained with the lecithin gels was about one order of magnitude higher than that obtained with an aqueous solution of the drug at the same conc. In contrast, the transport rates of scopolamine obtained with the micro emulsion solution prior to gelation (molar ratio of water to lecithin, 0) were not different from those obtained with the gel. The same variations in transport rates were observed for broxaterol in which case the flux through the skin was directly proportional to the conc. of drug in the gel. At a conc. of broxaterol of 75 mg/ml in the donor gel, the flux was $47 \mu\text{g h}^{-1} \text{cm}^{-2}$. Because preliminary results showed that transdermal transport is successful with amino acids and peptides also, it was concluded that lecithin gels maybe efficient vehicles for the transdermal transport of various drugs.

Airaksinen, L., Venalainen, et al., "Ketoprofen 2.5% gel versus placebo gel in the treatment of acute soft tissue injuries", *T. J. Clin. Pharm. Therap. & Toxicol.*, 31, 561-563 (1993).

A parallel double-blind placebo-controlled and randomized clinical study in a single centre was done with 2.5% ketoprofen gel in treating soft tissue injuries. Patients applied the gel twice daily for 7 days. Assessments were made on the 3rd and 7th days. The study group consisted of 29 patients and 27 patients in the control group. Pain at rest was significantly relieved in the ketoprofen group whereas the difference was insignificant in the placebo group. No difference in side effects was noticed between the groups. Thus, ketoprofen gel appears to be safe and superior to placebo in the treatment of soft tissue injuries.

Peacock, M., Rapier, C., "The topical NSAID felbinac is a cost effective alternative to oral NSAIDs for the treatment of rheumatic conditions", *Brit. J. Med. Econ.*, 6, 135-142 (1993).

A cost-effectiveness analysis was conducted to compare the basic drug cost, the shadow cost (treatment of peptic ulcers) and the total cost of treating 1000 patients with a month's supply of either an oral NSAID, the topical NSAID, Traxam (Lederle Labs, UK), or the combination product Arthrotec (diclofenac/misoprostol, Searle). A published treatment decision model was used to assess the costs associated with developing an ulcer due to NSAID treatment. The model showed that the shadow cost of treating the peptic ulcers resulting from administration of oral NSAIDs far outweighed the basic cost of these drugs. The large difference in the total treatment costs of oral NSAIDs and Traxam suggests that significant cost savings for both hospital and GP budgets could be made if the topical NSAID, Traxam was prescribed instead of an oral preparation.

Singh, P. and Roberts, M. S., "Skin Permeability and Local Concentrations of Nonsteroidal Anti-inflammatory Drugs after Topical Application", *J. Pharmacol. Exptl. Therap.*, 268, 144-151 (1994).

The human epidermal permeabilities of different NSAIDs (salicylic acid, diethylamine salicylate, indomethacin, naproxen, diclofenac and piroxicam) from aqueous solutions was found to be dependent on the drugs lipophilicity. The extent of local delivery of NSAID was assessed by comparing the tissue concentrations obtained below a treated site to those in contralateral tissues. The estimated tissue concentrations after epidermal applications of NSAIDs could be related to their maximal fluxes across epidermis from an applied vehicle.

Hosie, G. and Bird, H., "The Topical NSAID Felbinac versus Oral NSAIDs: A Critical Review", *Europ. J. Rheumatol. Inflamm.*, 14, 21-28 (1994).

Four separate multicentre, double-blind, double-dummy clinical trials have shown that the efficacy of the topical NSAID, felbinac, is equivalent to that of the oral NSAID, ibuprofen, in the treatment of soft tissue injuries, and to that of oral ibuprofen or fenbufen in mild to moderate osteoarthritis. Because of the gastrointestinal problems associated with oral NSAIDs the cost of treatment with topical felbinac is more economical for reasons of efficacy and safety.

Halpern, S. M., "Topical non-steroidal anti-inflammatory drugs: a review of their use and toxicity", *J. Dermatol. Treat.*, 5, 103-107 (1994).

NSAIDs are generally well-tolerated and have proved to be efficacious in arthritis and soft tissue injuries with a much reduced risk of adverse effects compared to their systemic counterparts. Established side-effects include local irritation with erythema or dermatitis, and urticarial reactions can occur with all preparations. Photocontact dermatitis is also well recognized especially with ketoprofen and benzydamine. Systemic reactions, particularly gastrointestinal disturbance and asthma, occur occasionally.

Campbell, J. and Dunn, T., "Evaluation of topical ibuprofen cream in the treatment of acute ankle sprains", *J. Accid. Emerg. Med.*, 11, 178-182 (1994).

One hundred patients who presented to the accident and emergency department with an acute ankle sprain were entered into a study to determine the efficacy of topical ibuprofen cream by using a double-blind placebo controlled design in a single type of soft-tissue injury. The subjects were given either topical ibuprofen cream or a placebo cream in addition to the standard management of the department. Patients kept diaries recording walking ability and pain visual analogue scales for resting, standing and walking. A total of 51 patients returned diaries that were suitable for analysis. Patients using the topical ibuprofen cream had significant reduction in pain scores over the first 48 h of treatment.

Evans, J. M. M. and MacDonald, T. M., "Tolerability of Topical NSAIDs in the Elderly", *Drugs and Aging*, 9, 101-108 (1995).

The purpose of topical NSAIDs is to achieve a high local concentration of the active ingredient at the affected site, with as low a plasma concentration as possible to minimize possible systemic adverse effects. The elderly seem to be more sensitive to the adverse effects of NSAIDs than younger individuals, and this may also be true for topical NSAIDs.

Evans, J. M. M., McMahon, A. D., McGilchrist, M. M., White, G., Murray, F. E. McDevitt, D. G. and MacDonald, T. M., "Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study", *Brit. Med. J.*, 311, 22-26, (1995).

The population studied was 319,465 people over a 6-year period. Conclusion: In this study topical non-steroidal anti-inflammatory drugs were not significantly associated with upper gastrointestinal bleeding and perforation after adjustment for the confounding effects of concomitant use of oral anti-inflammatories and ulcer healing drugs.

Heyneman, C. A., "Topical Nonsteroidal Antiinflammatory Drugs for Acute Soft Tissue Injuries", *Ann. Pharmacotherap.*, 29, 780-782 (1995).

Patient ratings of topical administration of commercial forms of felbinac, ibuprofen, piroxicam, ketoprofen and indomethacin indicated a superior efficacy of topical NSAIDs over placebo. Topical indomethacin is as effective as therapeutic doses of oral indomethacin.

Grahame, R., "Transdermal non-steroidal anti-inflammatory agents", *Brit. J. Clin. Pract.*, 49, 33-35 (1995).

There is a growing body of evidence attesting to the efficacy of topical NSAIDs in the treatment of acute soft-tissue injury and chronic soft-tissue overuse lesions. In one study of the latter, their use cut the need for local hydrocortisone injection by 50%. Topical NSAIDs may, therefore, be seen as an effective alternative to local steroid injection in cases of soft-tissue rheumatism, either where the injection is not acceptable to the patient or where the doctor has not acquired the necessary techniques. The safety profile of topical NSAIDs is good. Skin reactions are rare, and this apparently applies to all topical NSAIDs currently available. It is logical to treat a local pathological lesion with a local therapy, provided the agent is delivered effectively and sagely to the target organ or tissue. Where this can obviate the risk of life-threatening complications such as gastric hemorrhage, the case for substituting local for systemic medication is overwhelming.

Dreher, F., Walde, P., Walther, P., Wehrli, E., "Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport", *J. Control. Rel.*, 45, 131-140 (1997).

A soybean lecithin microemulsion of isopropyl palmitate and a small amount of water was studied as a matrix for transdermal drug delivery. The percutaneous absorption of indomethacin and diclofenac dissolved in the gel system resulted in steady-state fluxes of about $1 \mu\text{g h}^{-1} \text{cm}^{-2}$. Interaction studies were performed using Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and low-temperature scanning electron microscopy. These studies indicated that the lecithin gel, particularly in isopropyl palmitate, affects the stratum corneum lipid organization even after 1-day incubation. In vivo human skin irritation tests showed no significant irritancy.

Vaile, J. H., Davis, P., "Topical NSAIDs for Musculoskeletal Conditions. A Review of the Literature", *Drugs*, 56, 783-799 (1998),

In recent years, an influx of topical NSAIDs has appeared due to a high incidence of serious gastrointestinal adverse events associated with systemic NSAIDs and the premise that minimization of plasma concentrations of active drug may result in fewer systemic adverse effects. Evidence in humans and animals with topical NSAIDs demonstrates lower plasma concentrations than with systemically administered drugs, while those in soft tissues are still of a magnitude considered consistent with exerting an anti-inflammatory effect. In joints, however, the evidence is less strong, and there is still dispute whether in this case the drug reaches the joint predominantly via the transcutaneous or systemic route. Studies of soft tissue conditions have demonstrated superiority of topical NSAIDs over placebo and suggest equivalent efficacy in comparison with oral NSAIDs. The results are less convincing in the treatment of arthritic conditions and more clinical trials are required. The adverse event profile of topical agents is reasonable: minor cutaneous effects occur in up to 2% of patients but tend to be self-limiting. GI events appear to be infrequent and minor, although long term studies are required. The initial costs of topical agents tend to be higher than those of oral agents but a cost-effectiveness analysis suggests an overall benefit.

Bareggi, S. R., Pirola, R., De Benedittis, G., "Skin and plasma levels of acetylsalicylic acid: a comparison between topical aspirin/diethyl ether mixture and oral aspirin in acute herpes zoster and postherpetic neuralgia", *Eur. J. Clin. Pharmacol.*, 54, 231-235 (1998).

Skin and plasma levels of ASA and SA after topically administered ASA/diethyl ether mixture (ADE) in acute herpetic neuralgia and postherpetic neuralgia. Oral ASA (500 mg) or topical ADE (750 mg) were administered to 19 patient and the analgesic effect was assessed by means of a visual analogue scale (VAS). After ADE application, the analgesic effect was very rapid and VAS scores were lower than at baseline. Pain significantly decreased by 82.6% after topical and 15.4% after oral ASA. After ADE, 95% of the patients had excellent or good pain relief, but after oral administration 79% had a poor response. Skin concentrations of ASA, but not SA, after ADE were about 80-

to 100-fold those after oral administration. Levels of ASA and SA in plasma after oral administration were similar to those previously found, but after ADE were undetectable or very low. Patients with excellent pain relief showed a trend towards higher ASA skin concentrations. **CONCLUSION:** The analgesic effect can be obtained only after topical administration because by this route the skin levels of ASA are much higher than after oral administration. The mechanism is exclusively local; there are no active drugs in plasma after topical administration.

Grace, D., Rogers, J., Skeith, K., Anderson, K., "Topical diclofenac versus placebo: a double blind, randomized clinical trial in patients with osteoarthritis of the knee", *J. Rheum.*, 26, 2659-2663 (1999).

Seventy patients completed a double blind, randomized, placebo-controlled, parallel group design 2 week clinical trial to determine the efficacy of topical 2% diclofenac in lecithin organogel (PHLOJEL) in the treatment of pain associated with mild to moderate osteoarthritis (OA) of the knee. Patient responses to disease-specific (WOMAC VA3.0) total score and aggregated subscale scores revealed significant improvement ($p < 0.5$) on the aggregated total score and the pain, stiffness, and physical function subscales from baseline to post-treatment for the active treatment group compared to the placebo group. Analysis of gain scores also revealed significant improvement with active versus placebo treatments. Other efficacy measures exhibited no significant differences between or within treatment groups. Thus, a topical formulation of 2% diclofenac in a lecithin organogel appears to have therapeutic value in patients with mild to moderate OA of the knee as determined by responses from the WOMAC osteoarthritis health status measure.

Rosenstein, E. D., "Topical agents in the treatment of rheumatic disorders", *Rheum. Dis. Clin. North Am.*, 25, 899-918 (1999).

Topical drug delivery may be the optimal route for the treatment of localized musculoskeletal disorders because higher drug concentrations can be achieved at the sites of clinical significance. The rationale for the use of topical NSAIDs and capsaicin in the treatment of soft-tissue rheumatic complaints and osteoarthritis of selected joints is reviewed. Although there are extensive, uncontrolled experiences with DMSO that suggests its effectiveness in the treatment of musculoskeletal disorders, controlled trials yield conflicting results. The basis for the use of physical modalities such as phonophoresis and iontophoresis to improve topical drug delivery is summarized.